History will teach us something - immune system examples of the effects of different scales of selection pressure,

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The population of B cells in our body comprised of ~ 10^ 9 different clones. The progenitor of each clone is selected for receptor function following a unique recombination of its V(D)J gene segments. Thus each clone has their own sets of specific B cells receptors, which are further diversified through mutation and selection during immune responses. I will present two studies that show how by considering the patterns of mutation, diversification and expansion of B cell clones we can tease out conditions in the body where selection differs and how it can influence diversification and selection across multiple time scales. The B cell clone is uniquely suited for such analysis as, unlike in most studies of gene evolution, we can identify both the mutant and it's germline source. Analyzing high throughput sequencing experiments that allowed us to consider millions of clones from tens of individuals in different human populations I will describe the clear division of B cell repertoires between gut and blood tissues as well as the special influence of serine codon usage on serine substitutions patterns. The latter of which influences both somatic and germline selection process in B cells but also in general in evolution.

Reading materials:
http://simlab.biomed.drexel.edu/papers_published/atlas.pdf
http://rstb.royalsocietypublishing.org/content/370/1676/20140243
http://simlab.biomed.drexel.edu/papers_published/11Proc._Natl._Acad._Sci._U.S.A._2006_Hershberg.pdf
https://www.nature.com/articles/225563a0

Questions –

1. What is the common unit of selection? How do we define a clone?
2. How can we differentiate between selection and the effects of mutation?
3. What kinds of selection exist? What is the function being selected?
4. Do B cell clones expand equally throughout the body?
5. Is there a tissue specific selection?

From Boom to bust - the dynamics of bacterial adaptation under prolonged resource limitation

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Many bacteria, including the model bacterium Escherichia coli can survive for years within spent media, following resource exhaustion. We carried out evolutionary experiments, followed by full genome sequencing of hundreds of evolved clones to study the dynamics by which E. coli adapts during the first four months of survival under resource exhaustion. Our results reveal that bacteria evolving under resource exhaustion are subject to intense selection, manifesting in rapid mutation accumulation, enrichment in functional mutation categories and extremely convergent adaptation. Our results further demonstrate that such adaptation is not limited by mutational input. Indeed, mutational input appears to be high enough to enable bacteria to rapidly adapt, in a highly convergent manner and with great temporal precision through fluctuations in allele frequencies. Finally, we demonstrate that due to antagonistic pleiotropy and mutation accumulation, survival under resource exhaustion can severely reduce a bacterium's ability to grow exponentially, once resources are again available. We study how this affects the ability of bacterial populations to re-adapt to growth once resources again become available. Combined, our results shed light on bacterial adaptation to long-periods of resource exhaustion and on the consequences such adaptation has on the genetic makeup of individual bacteria and on patterns of genetic variation within bacterial populations.

General question: How do bacteria adapt to survive under prolonged resource exhaustion and with what consequences on individual bacteria and on the entire bacterial population?

Specific questions:

1. To what extent does survival under resource exhaustion require genetic adaptation?
2. Is adaptation under resource exhaustion limited by mutation input?
3. How quickly and in what manner do resource exhausted bacterial population re-adapt to growth once resources again become available?

Suggested reading: Avrani et al (2017) Rapid Genetic Adaptation during the First Four Months of Survival under Resource Exhaustion. Molecular Biology and Evolution (https://academic.oup.com/mbe/article/34/7/1758/3091892)

Signaling molecules in human immunologic diseases: Basic lessons in immunology and inflammation from rare patients.

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Monogenic disorders have long been utilized as models to identify and then study focal pathways involved in biological processes and how they relate to human health and disease. These “experiments of nature” provide opportunities for immunologists as well. Recently identified lessons in antigen receptor and cytokine signaling pathways have opened a trove of insight into a vast array of medically relevant physiologic pathways-- from the role of magnesium as a second messenger in T-cell receptor signaling in EBV infection to the surprisingly limited single-infection phenotype seen in patients with defects in toll-like receptor signaling molecules. Infectious susceptibility is not the only consequence of many of these monogenic disorders of the immune system. Atypical inflammatory responses – such as the “cold abscesses” seen in STAT3 loss of function mutations, rare or severe allergies -- such as cold urticaria seen in PLCG2 deletions or dermatitis in dominant negative CARD11 mutations, predisposition to multiple early onset autoimmune conditions -- such as STAT3 gain of function mutations, and cancers -- seen in STAT1 gain of function mutations have revealed insight into pathways relevant to common diseases and phenotypes. In studying these diseases, focal pathway specific treatments are being developed, which may be used both to treat these rare patients, but also to manage common conditions as well.

Reading materials:

https://www.ncbi.nlm.nih.gov/pubmed/29549114
https://www.ncbi.nlm.nih.gov/pubmed/28710273
https://www.ncbi.nlm.nih.gov/pubmed/26948077

Research questions:

1. Patients don’t read the book: How do individual monogenic diseases affecting the immune system cause both impaired host defense and exaggerated immune responses simultaneously?
2. Mutations don’t always change the host for the worse: Are monogenic immune-related syndromes always deleterious?
3. Mutations don’t happen in a vacuum: What are the collateral pathological and non-pathological consequences of focal lesions in signaling pathways?

TCR repertoires of tumor infiltrating T cells in metastatic breast cancer

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Abstract:

Breast cancer is the most prevalent cancer in women around the world, accounting for 30% of all new cancer cases in women in the US. In this study, we examine genetic and immunological data from eight breast cancer patients who had died from metastatic breast cancer, focusing on the T cell response to the metastases. This response is mediated by tumor infiltrating lymphocytes (TILs). We capture a sample of the T cell repertoire in the metastases by sequencing the alpha and beta chains of T cell receptors, found on TILs inside the different metastases, using high-throughput sequencing (TCRSeq).

We start by studying classic notions of TCR repertoires like sharing, expansion and convergent recombination and show the role they play in shaping the metastatic repertoire. Next, by using unsupervised learning techniques we are able to show that the T cell response has a distinct organ-specific signature, i.e., it is more similar in metastases in the same organ than in metastases in different organs. We also show that there is a high correlation between the organization of the T cell response, and the mutational landscape of breast cancer as captured by a phylogenetic model of the evolution of patient's metastases. Finally, we present an interesting statistical framework for pairing between alpha and beta chains.

This work has interesting consequences for designing new T cell based immune-therapies. Especially, it shows that any therapy of this kind should take into account the different immune signature of metastases in different organs.

Leading Questions:

What can we learn from TCR repertoires of TILs? How can we infer escape mechanism like HLA loss or B2M loss from repertoire data? How can we connect data regarding the mutational landscape of cancer (SNVs) to the immune response? Moreover, what are the roles of convergent recombination and sharing in the metastatic repertoire within the same patient?

Suggested reading:

1. Madi A, Shifrut E, Reich-Zeliger S, et al. T-cell receptor repertoires share a restricted set of public and abundant CDR3 sequences that are associated with self-related immunity. *Genome Res*. 2014;24(10):1603-1612.

2. Madi A, Poran A, Shifrut E, et al. T cell receptor repertoires of mice and humans are clustered in similarity networks around conserved public CDR3 sequences. Chakraborty AK, ed. *Elife*. 2017;6:e22057. doi:10.7554/eLife.22057.

3. Geukes Foppen MH, Donia M, Svane IM, Haanen J. Tumor- infiltrating lymphocytes for the treatment of metastatic cancer . Olweus J, ed. *Mol Oncol*. 2015;9(10):1918-1935. doi:10.1016/j.molonc.2015.10.018.

From sensory perception to foraging decision making - the bat's point of view

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Bats are remarkable aviators and amazing navigators. Many bat species nightly commute dozens of kilometres in search of food, and some bat species annually migrate over thousands of kilometres. Studying bats in their natural environment has always been extremely challenging because of their small size (mostly <50 gr) and agile nature. In the past four years, we have developed novel miniature technology to GPS-tag small bats, thus opening a new window to document their behaviour in the wild. However, the movement of an animal alone is not sufficient for studying its behaviour and its decision processes. We therefore equipped our miniature GPS devices with an ultrasonic microphone, which allows monitoring the sonar and social communication of freely behaving bats. Because echolocating bats rely on sound emission to perceive their environment, on-board recordings enable us to tap into their sensory 'point of view' and to monitor fundamental aspects of their behaviour such as attacks on prey and interactions with conspecifics. This intimate description of behaviour allows us to examine sensory decision making under natural conditions. In my talk, I will present several projects that examined how bats combine sensory information with social information in order to improve foraging. I will also present our current effort to include more on-board sensors for the study of bat Neuro-Ecology including acceleration, EEG and physiology sensors.

Questions:
1) How do animals make decisions in the real world?
2) How do they decide where to move?
3) How do they decide with whom to move?

Refferences:

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P. Kounitsky, J. Rydell, E. Amichai, A. Boonman, O. Eitan, A. J. Weiss, Y. Yovel (2015) Bats adjust their mouth gape to zoom in their biosonar 'field of view' *Proc. Natl. Acad. Sci. USA, 112 (21), 6724-6729*

G. Aharon, M. Sadot, Y. Yovel (2017) Bats use path-integration rather than acoustic- flow to assess flight distance along flyways. *Current Biology 27,* 1-8